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Award Number: DAMD17-98-1-8333

TITLE: Inherited Susceptibility to Breast Cancer in Healthy
Women: Mutation in Breast Cancer Genes, Immune
Surveillance, and Psychological Distress

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REPORT DATE: October 2002

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

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20030214 255

REPORT DOCUMENTATION PAGEForm Approved
OMB No. 074-0188

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302, and to the Office of Management and Budget, Paperwork Reduction Project (0704-0188), Washington, DC 20503

1. AGENCY USE ONLY (Leave blank)		2. REPORT DATE October 2002	3. REPORT TYPE AND DATES COVERED Annual (28 Sep 01 -27 Sep 02)	
4. TITLE AND SUBTITLE Inherited Susceptibility to Breast Cancer in Healthy Women: Mutation in Breast Cancer Genes, Immune Surveillance, and Psychological Distress			5. FUNDING NUMBERS DAMD17-98-1-8333	
6. AUTHOR(S): Dana H. Bovbjerg, Ph.D.				
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Mount Sinai School of Medicine New York, New York 10029-6574 E-Mail: dana.bovbjerg@mssm.edu			8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012			10. SPONSORING / MONITORING AGENCY REPORT NUMBER	
11. SUPPLEMENTARY NOTES				
12a. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited				12b. DISTRIBUTION CODE
13. Abstract (Maximum 200 Words) (abstract should contain no proprietary or confidential information) The purpose of the research supported by this IDEA grant award, is to provide the first critical test of the possibility that variability in the strength of immune surveillance mechanisms against cancer (operationally defined by assessment of natural killer cell activity) may be a factor in determining the penetrance of mutations in breast cancer susceptibility genes. Two possible explanations for variability in NK cell activity are being investigated: 1) stress-induced immune suppression, and 2) inherited deficits in immune surveillance. To date, largely as a result of challenges posed by a change in study site associated with a new academic position for the PI, the study has fallen substantially behind anticipated recruitment levels. As we have husbanded resources, while addressing these challenges, we anticipate being able to meet study goals over the next year. We have therefore requested a no-cost extension of the award.				
14. SUBJECT TERMS breast cancer, mutations, cancer genes, psychological distress				15. NUMBER OF PAGES 6
				16. PRICE CODE
17. SECURITY CLASSIFICATION OF REPORT Unclassified	18. SECURITY CLASSIFICATION OF THIS PAGE Unclassified	19. SECURITY CLASSIFICATION OF ABSTRACT Unclassified	20. LIMITATION OF ABSTRACT Unlimited	

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INTRODUCTION:

Accumulating evidence indicates that modifying genes and/or environmental factors are likely to have a major impact on the expression of mutations in the recently identified breast cancer genes (BRCA1/BRCA2). The factors responsible for such differences in the penetrance of mutations in these primary susceptibility genes are not yet known. To date, speculation concerning these modifying factors has focused only on the usual suspects - hormonal/reproductive variables, which have already been shown in large scale epidemiological studies to be independent risk factors for the development of breast cancer independent of family history of the disease. Some risk factors for breast cancer, however, are likely to have an impact only in conjunction with mutations in primary susceptibility genes. Such factors, by themselves, might go undetected in standard epidemiological studies, but would become evident when examined in conjunction with testing for primary susceptibility genes. The purpose of the research supported by this IDEA grant award, is to provide the first critical test of possibility that variability in the strength of immune surveillance mechanisms against cancer (operationally defined as natural killer cell activity) may be a factor in determining the penetrance of mutations in breast cancer susceptibility genes. Two possible explanations for variability in NK cell activity are being investigated: 1) stress-induced immune suppression, and 2) inherited deficits in immune surveillance. In addition, we are examining the possibility that inherited deficits in immune surveillance may be independently associated with familial risk of breast cancer. The study "piggie-backs" on other ongoing studies involving genetic counseling and breast cancer gene testing at Mount Sinai Medical Center under the direction of Co-Investigators on this proposal. The participants are recruited to three Study Groups (N=100/group) of comparable age for the research: 1) The Mutation-Positive Family History Group (Mut+Hist+) includes women whose family histories of cancer indicate a relative risk ≥ 1.5 for breast cancer and who carry a mutation in BRCA1 or BRCA2; 2) The Mutation-Negative Risk Family History Group (Mut-Hist+) includes women with comparable family histories, who do not carry mutations; 3) The Normal Risk Group (Mut-Hist-) includes women without family histories of cancer who are known not to carry mutations. Each participant is assessed on three separate occasions (at the same time of day): 1) immediately prior to notification of the results of their gene testing; 2) one month later; 2) three months later. Consistent with scheduling exigencies, one woman from each group is concurrently assessed, by personnel "blind" to group status. At each assessment, standardized self-report measures are completed, a blood sample (40 ml) is collected (as feasible), and \$23 reimbursement offered.

BODY:

As of this reporting period, no results are yet available from this study. We have fallen substantially behind the proposed rate of study accrual for reasons related to a change in employment for Bovbjerg (PI) and Valdimarsdottir (Co-invest.) which required a change in study site from Memorial Sloan-Kettering Cancer Center to The Mount Sinai Medical Center. The change in study site in turn required modification of collaborative arrangements (e.g., the addition of Eng as a co-investigator), set up of new facilities (e.g., Bovbjerg lab), hiring of new support staff, and additional attention to institutional review requirements. Eng has subsequently left Mount Sinai and Valdimarsdottir has begun a new collaborative study involving investigators at another institution (Georgetown) necessitating further modification of collaborative arrangements. As a result of these considerations, no subjects have completed the entire set of proposed study assessments, as of this annual review date. During this reporting period, however, the proposed psychological assessments of stress associated with familial risk and genetic testing have been conducted with 21 women (for a total of 93), as a way for us to collect some of the proposed data prior to having all collaborations fully implemented and the laboratory on line. We have now addressed the initial challenges posed by the transition of key members of the research team to a new institution, and have addressed the critical loss of Eng by the addition of a new Co-investigator who is an Associate Professor of Human Genetics (Margaret McGovern, M.D., Ph.D.). In addition, further facilitating our recruitment efforts and coordination of the research data collection with the clinical provision of genetic counseling, we have added the Director of Cancer Genetic Counseling at Mount Sinai (Karen Brown, M.S., C.G.C) as an additional Co-investigator. Facilitating the timely and rigorous completion of the proposed immune assessment battery, Bovbjerg's laboratory is now headed by a dedicated, highly skilled, immunologist (Jan Jeremias, M.S.), who has also been added as a

Co-investigator on the project. Also facilitating recruitment to the study is the recent hiring by Valdimarsdottir of a full-time cancer genetics counselor, who has dramatically enhanced recruitment to the related studies involving BRCA testing and counseling that are a source of potential participants for our study. Thus, with an increased pool of potential participants for the study as a result of research and clinical efforts by the current team of Co-investigators on the study, and having husbanded our resources, we anticipate making very strong progress during the next year.

PROPOSAL:

We therefore request a no-cost extension of the grant to allow us to address the study aims over the course of the next year. The Hypotheses and Technical Objectives, as well as the basic study design of the research project will remain unchanged from the original approved grant. The Methods and statistical analyses will also remain the same with Three modest methodological changes are proposed to enhance the feasibility of completing the research expeditiously. First, we propose to reduce the sample size to 80 per group from 100, which should have little effect on statistical power, as preliminary data from other studies has revealed a stronger effect size than originally anticipated. Second, we propose to enhance recruitment efforts by making the scheduling of three assessment days more convenient for the participants and more feasible for the investigators by: a) not specifically linking the timing of the first assessment to the timing of notification, and b) by allowing more flexibility in the scheduling of the subsequent two assessments. Third, we propose to streamline the immune assessments by using well validated and reliable whole blood approaches (e.g., four color flow cytometry), rather than approaches requiring labor intensive isolation of peripheral blood lymphocytes.

KEY RESEARCH ACCOMPLISHMENTS:

At this point in the research no results are yet available.

REPORTABLE OUTCOMES:

Department of the Army (Bovbjerg, PI) (Valdimarsdottir, Project 2 PI) (Brown, McGovern, Co-Inv)	7/1/01 - 6/30/05 \$375,099	15%
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Center Grant: Genetic Factors in Breast Cancer: Center for Interdisciplinary Biobehavioral Research:
Project 2: "Impact of culturally tailored counseling on psychobehavioral outcomes and BRCA
decision making among women with breast cancer"(Valdimarsdottir, PI)

National Cancer Institute (Valdimarsdottir, PI) (Bovbjerg, Co-Inv)	12/1/02 - 11/30/07 \$475,935	30%
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Decisions & Outcomes of BRCA 1/2 Test for Breast Patients

American Cancer Society
(Valdimarsdottir, PI)
(Bovbjerg, Co-Inv)

1/1/03 - 12/31/06

5%

BRCA Counseling/Testing for Urban African American Women

Department of the Army
(Bovbjerg, PI)

7/1/02 - 6/30/07

5%

Immune Surveillance, Cytokines and Breast Cancer Risk: Genetic and Psychological Influences in African American Women

CONCLUSIONS:

At this point in the research, no results are yet available. If results of the proposed research are consistent with the hypothesis that deficits in immune surveillance (e.g., as a result of stress) moderate the effects of mutations in primary susceptibility genes, the study could have important implications for the eradication of breast cancer. Such results would raise the possibility that appropriate interventions to reduce stress and increase the activity of immune surveillance mechanisms in women carrying mutations in primary susceptibility genes might delay the onset or prevent the development of breast cancer.